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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

# Translating Stem Cell Research to Cardiac Disease Therapies

## Pitfalls and Prospects for Improvement

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**ABSTRACT**

Over the past 2 decades, there have been numerous stem cell studies focused on cardiac diseases, ranging from proof-of-concept to phase 2 trials. This series of papers focuses on the legacy of these studies and the outlook for future treatment of cardiac diseases with stem cell therapies. The first section by Drs. Rosen and Myerburg is an independent review that analyzes the basic science and translational strategies supporting the rapid advance of stem cell technology to the clinic, the philosophies behind them, trial designs, and means for going forward that may impact favorably on progress. The second and third sections were collected as responses to the initial section of this review. The commentary by Drs. Francis and Cole discusses the review by Drs. Rosen and Myerburg and details how trial outcomes can be affected by noise, poor trial design (particularly the absence of blinding), and normal human tendencies toward optimism and denial. The final, independent paper by Dr. Marbán takes a different perspective concerning the potential for positive impact of stem cell research applied to heart disease and future prospects for its clinical application. *(Compiled by the JACC editors)* (J Am Coll Cardiol 2014;64:922–37) © 2014 by the American College of Cardiology Foundation.

## TRANSLATING STEM CELL RESEARCH TO THE TREATMENT OF CARDIAC DISEASE

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Over the past 5 decades, cardiovascular medicine has advanced through the melding of diverse scientific and technical concepts. Strategies for prediction, prevention, intervention, molecular genetics, and regeneration have been tested for clinical relevance and applicability by various risk profiling and clinical trial techniques. One of the more recent of these strategic concepts is regenerative therapy, which targets repair or replacement of lost or dysfunctional

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substrates. Regenerative strategies have moved rapidly to clinical application for subsets of patients, including those with heart disease, and during the past 2 decades, thousands of patients have been administered various types of stem cells in clinical cardiac disease studies ranging from proof-of-concept to phase 2 trials. These clinical cardiac applications have focused in part on patients for whom preventive and conventional intervention strategies failed to avert cellular depopulation, leading to intractable clinical consequences. However, a far broader population has received stem cells, including patients for whom traditional therapies have proven effective (1), and outcomes have been conflicting.

This paper is not intended as a thorough literature review of the field. Rather, we are analyzing the basic science and translational strategies supporting the rapid advance of stem cell technology to the clinic, the philosophies behind the strategies, the positive and negative aspects of trial designs reported, and the means for going forward that may impact favorably on progress. The analysis is provided in the context of the complex scientific, clinical, ethical, and fiscal considerations that are affected by this evolving field of interest.

**THE PAST AS PROLOGUE…CARDIOVASCULAR MORBIDITY AND MORTALITY.** It is useful to consider the emergence of stem cell therapy against the background of the evolution of cardiovascular disease outcomes in the past one-half century. Between the mid-20th century and the turn of the millennium, a major reduction in cardiovascular mortality (attributable to advances predating stem cell therapy) occurred in the United States and elsewhere. For example, the National Heart, Lung and Blood Institute reported a 49% reduction in age-adjusted mortality from coronary heart disease between 1950 and 1998 (2). As a mortality rate adjusted for age, this reflects prolongation of life expectancy and not necessarily an equivalent absolute reduction in total population mortality. One major contributing factor was the dramatic transition from a 30% acute myocardial infarction (AMI) death rate prior to coronary care units, to <10% with interventional therapies in the later 1990s (3), and even lower currently (4).

The reduction in AMI deaths led to a survivor cohort at risk for and characterized by the emergence of an increasing population burden of chronic heart failure. Development and refinement of various heart failure prevention and treatment strategies (none of which depend on stem cell therapy) are reflected in American Heart Association statistics revealing continued improvements in patient survival. An example is the 33% fall in death rates from heart failure and stroke between 1999 and 2009 (5). This does not argue against the potential added value of stem cell therapy for improving survival and quality of life. But, it does demand that we provide solid scientific underpinnings for incremental outcomes being suggested to the public.

**DIVERGENT OPINIONS REGARDING PRESENT AND FUTURE DIRECTIONS.** These advances, along with the remaining challenges and dichotomies that sometimes exist between basic and clinical research, have led to divergent viewpoints regarding advancement of cardiovascular stem cell therapies into the clinic. Such viewpoints expressed by leaders in the field were published 10 years ago (6) and are paraphrased here:

1. *"We do not…know what cell to use in any given situation…until we do, we shouldn't go forward clinically;"*
2. *"The science of clinical stem cell trials isn't sufficiently mature to warrant large-scale clinical studies;"*
3. *"The stem cell literature is too internally contradictory to provide a clear vision for going forward;"*
4. *"Patients who are dying and are desperate to live should be availed of experimental stem cell therapies;"* and
5. *"The field is sufficiently mature that within 3-5 years, stem cells will have favorably altered the clinical course of major cardiovascular disease"* (6).

We shall now revisit these viewpoints in the context of the clinical translation that has occurred during the decade since they appeared and discuss models and approaches for consideration as we move into the next decade.

**"WE DO NOT KNOW WHAT CELL TO USE…" (6).** There is substantial literature regarding stem cells (7–10), and a number of stem cell types described in this literature have been administered to patients. Stem cells may be pluripotent (i.e., capable of differentiating into literally any cell type in the body) or multipotent (i.e., in lineages downstream of pluripotency and destined to differentiate into more circumscribed mature cell populations). Pluripotent cells include human embryonic stem cells and induced pluripotent stem cells (7); the latter are derived from adult cells using oncogenic or nononcogenic transcription factors (11–15). Both cell types have been reprogrammed into mature lineages, including cardiac myocytes. Although both pluripotent cell types are

**ABBREVIATIONS AND ACRONYMS**

**AMI** = acute myocardial infarction

**BMMC** = bone marrow–derived mononuclear cell

**CDC** = cardiosphere-derived cell

**EF** = ejection fraction

**LVEF** = left ventricular ejection fraction

**MI** = myocardial infarction

**MSC** = mesenchymal stem cell

currently in clinical studies (16,17), neither of these 2 studies address cardiovascular therapy. However, induced pluripotent stem cells are providing an experimental tool for studying human cardiovascular disease genetics (e.g., Terrenoire et al. [18]).

Most human cardiac trials have employed multipotent cells—autologous or allogeneic mesenchymal stem cells (MSCs) or bone marrow-derived mononuclear cells (BMMCs) (8). Cardiospheres and c-kit$^+$ cells derived from subselection processes have been obtained from cardiac tissues and administered autologously (19,20). Skeletal myoblasts have been studied in clinical trials, but an association with potentially lethal arrhythmias and failure to see clear benefit has discouraged continuation (21).

A nagging concern in the stem cell field has been the possibility of a disastrous event, analogous to that experienced with viral vectors employed in the early days of gene therapy. Although it seemed for a while that the safety of MSCs combined with promising results from a number of trials would preempt such an event, the recent identification of discrepancies in a number of clinical trials (22), coupled with retraction of data integral to clinical attempts at myocardial repair and regeneration (23), is promoting reassessment of the validity of our current knowledge base and approaches (24–26). Investigation into data retraction issues (23–26) is ongoing, and it would be inappropriate to speculate on the outcome at this time. However, we hope that the final determinations will be made public in a timely fashion so that the meaning of what happened can be analyzed and the scientific and clinical communities can learn lessons and again move forward.

**Should we administer cells or cell products?** In the early days of stem cell research, it was generally assumed that the cells would themselves mature and propagate to regenerate/repair tissues. However, there are challenges (largely focused on cell fate) to this mindset, as noted in human studies suggesting that cell retention rates are low (reviewed in Bartunek et al. [27]). Cell retention is in part influenced by route of administration, with conflicting results reported for different routes. For example, patients with dilated cardiomyopathy of various etiologies given CD34+ cells by the intramyocardial route showed better cell retention at 18 h and a higher left ventricular ejection fraction (LVEF) at 6 months than those in whom the cells were administered by the intracoronary route (28). Other reports demonstrated that sites closest to the MSC intramyocardial injection locus show the greatest improvements in outcomes measured through 1 to 1.5 years, and these appear to be accompanied by secondary improvement in global function (29–31).

Because we lack long-term cell retention data, it is reasonable to ask whether stem cells and their progeny actually remain where injected to repopulate a myocyte-depleted myocardium or whether the stem cells release products that mobilize endogenous cardiac precursors. In some animal studies, various types of stem cells do not long remain where administered, but release paracrine factors that promote repair by mobilizing endogenous progenitors (32–38). Paracrine contributors under investigation include growth factors, cytokines, chemokines, bioactive lipids, and microvesicles (39–42).

Conceivably, identifying the "appropriate" paracrine factor(s) might lead to development of molecules more selective, specific, safe, and effective than transplanted stem cells, thereby suggesting pharmacological strategies for regeneration/repair (40). Alternatively, paracrine elements may be less effective without the stem cell as their vehicle. In the face of these uncertainties, a growing body of research focuses on the physiological interactions of native and donor cells with paracrine factors released by stem cells (43,44). The outcomes of this work may significantly influence future approaches to regenerative therapy.

**The impact of age.** Stem cells from older experimental animals (45) or human subjects (37–48) are not as robust as those from the young. Changing the environment in which stem cells of older individuals are maintained and propagated might yield a formula to improve their function. Absent this, allogeneic MSCs from young donors are potential sources with established safety (8,49). But if implanted cells function to recruit native progenitors, progenitors recruited in older individuals might not be as effective in healing and repair as those recruited in the young.

To summarize, despite tests of multipotent cells and their derivatives in a variety of animal models and clinical settings and despite clinical studies suggesting the potential of specific cells (8,19,20), not only is the identity of the "best cell" to use in any specific pathophysiological state still unknown, but also the knowledge base used to validate employment of certain cell types requires reconsideration as data considered to be significant are questioned and/or are retracted (23–26). While the need for extreme caution in study design is self-evident, careful analysis and interpretation of data on which clinical advancement is based are also critical to the viability of any field of clinical science.

**"THE SCIENCE OF CLINICAL STEM CELL TRIALS ISN'T SUFFICIENTLY MATURE TO WARRANT LARGE-SCALE CLINICAL STUDIES…" (6).** The history of cardiac stem cell (CSC) research and development from basic laboratory to clinical application is reminiscent of a cottage industry. Individual laboratories develop their own cells, approaches, and funding; protect their intellectual property; and advance to clinical trials as small businesses. A review of the literature reveals methodological heterogeneity in obtaining, standardizing, and administering cells, as well as in enrolling, analyzing, and tracking patients. The overall effort is multicentric and heterogeneous, lacking uniform design and consistent oversight (50).

**Limitations in current knowledge impacting CSC trials.** Clinical testing strategies range from rigidly controlled randomized trials to observational strategies for defining association, causation, clinical effects, and safety (Figure 1). Although clinical trial design would benefit from knowledge of the optimal cell types for specific cardiac therapeutic indications, we do not have that knowledge, nor have we been able to catalog the potential downsides of cell administration, the best way to prepare the cells, the impact of trying to subselect or modify them, and the best way to store, assay, or administer them (7,51–53). Disease models have been created in mice, dogs, and pigs, and observations are available from patients, but we are still in midstream with regard to optimizing therapy. It also remains unclear whether there is a single optimal therapeutic model versus several different models providing target-specific therapeutic benefits.

**Inconsistent standards for CSC trial enrollment.** Many cardiac patients participating in stem cell trials have had moderately-to-severely decompensated heart failure in the post-AMI or chronic ischemic heart disease setting (8,19,20,46). Even as data have accumulated indicating that older patients are less likely to benefit than younger ones and that patients with moderate decompensation benefit inconsistently, there are, as yet, no standardized stratification schemes for age or severity of left ventricular (LV) dysfunction. Some studies enroll patients with an ejection fraction (EF) >0.45. Although diastolic heart failure with a preserved EF is recognized to have increased mortality risk, it is not clear that repopulation therapy would be as beneficial to this category of patients as it would be to those with low EFs due to systolic heart failure. The pathological anatomy and pathophysiology of heart failure clearly differ between these 2 patient categories.

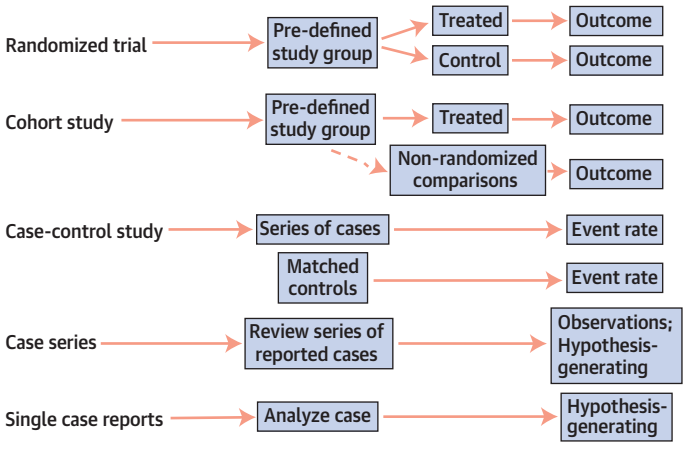


**FIGURE 1 Strategies to Evaluate Benefits of Therapy**

Clinical testing strategies range from rigidly controlled randomized trials to observational strategies for defining association, causation, clinical effects, and safety.

**"THE LITERATURE IS TOO INTERNALLY CONTRADICTORY TO PROVIDE A CLEAR VISION FOR GOING FORWARD…" (6). Contradictions confronted in reviewing individual clinical stem cell trials.** Most clinical trials of CSC therapy have administered autologous or allogeneic bone marrow-derived cells (8); some have used cells obtained from autologous myocardial tissues (19,20). Means of obtaining and administering stem cells also have differed, as have the selection of subsets of patients to whom they would be administered. Three recent studies using different numbers, types, and modes of administration of cells in varied patient settings are exemplary. We deliberately compare apples and oranges in highlighting these trials to focus attention on the questions that should arise when designing protocols or when reading and interpreting the emerging literature.

The FOCUS-CCTRN (Effect of Transendocardial Delivery of Autologous Bone Marrow Mononuclear Cells on Functional Capacity, Left Ventricular Function, and Perfusion in Chronic Heart Failure) trial (46) delivered 100,000,000 autologous BMMCs in a randomized, double-blinded study of 92 patients in chronic ischemic heart failure. At 6 months, no significant impact was noted on the primary endpoints ($MVO_2$, LV end-systolic volume, and reversible defect). An exploratory analysis showed a statistically significant, but physiologically limited, improvement in LVEF.

CADUCEUS (CArdiosphere-Derived aUtologous stem CElls to reverse ventricULar dySfunction) (19,54)

is described as a prospective, randomized, phase 1b safety trial. An initial dose escalation protocol assessed the safety of $CD105^{+}/CD45^{-}$ autologous mononuclear cells obtained from myocardial biopsies done 2 to 4 weeks after AMI and infused into the infarct-related artery 1.5 to 3 months post-infarction. Seventeen patients received 25,000,000 cells, whereas 8 control subjects received standard therapy. Cardiac function was unaltered, despite significant reductions in scar mass and increased viable heart mass, regional contractility, and regional systolic wall thickening. The same investigators are now recruiting 300 patients for a phase 1-2 trial using allogeneic cells (55) rather than the autologous cells employed in CADUCEUS.

SCIPIO (Administration of Cardiac Stem Cells in Patients With Ischemic Cardiomyopathy) (20) was reported as a randomized, open-label phase 1 trial in patients with ischemic heart disease and congestive failure undergoing coronary artery bypass grafting. Right atrial biopsies were obtained during surgery; 4 months later, 20 patients received 1,000,000 autologous $c\text{-}kit^{+}$ CSCs injected into the major vessel(s) supplying an infarcted region. LVEF in CSC recipients increased from 28% during control to 41% at 12 months. However, concerns regarding a preliminary report of the SCIPIO trial (26,56) and the retraction of a fundamental study of cardiac repair/regeneration potential (23) whose basic research data were reportedly "compromised" (24,25) have created uncertainty regarding these observations. Although it is claimed that the clinical SCIPIO data (56) are not compromised (24,25), the issue remains under review by the appropriate bodies and should not be prejudged prior to completion of the investigation.

The information presented in the previous text illustrates some fundamental problems besetting stem cell research. These problems are compounded by confusion deriving from the diversity of approaches and outcomes among the clinical trials. Arguably, the ideal phase 2 clinical trial is sufficiently powered, double-blinded, and randomized, with clearly defined and objectively identifiable primary and secondary endpoints (57). Of the 3 cited studies, FOCUS (46) was the only trial to achieve that standard, and it yielded the least positive outcome. The other trials are not directly comparable; they used different cells, modes of administration, patient populations, and more preliminary study designs, yet they received very positive coverage (58).

What we are best advised to do regarding studies like SCIPIO (20) or CADUCEUS (19) is await final reports while recalling the caveat that outcomes of relatively small studies are often misleading (59). This caveat is not unique to stem cell therapy; larger, randomized trials in other areas of cardiovascular medicine have not validated outcomes anticipated on the basis of dramatic results from small studies (60–62).

**Interpreting and reinterpreting the literature.** An analysis of 133 reports from 49 trials provides troubling insights into how stem cell trials are reported and the meaning of their outcomes (22). More than 600 discrepancies were noted. In an earlier analysis of 48 reports from a single group, 200 discrepancies were identified including "conflicts in recruitment dates, criteria, sample sizes…cell counts…fractional numbers of patients… arithmetical miscalculations, statistical errors, suppression of significant changes, exaggerated descriptions of findings, possible silent patient deletions…identical results with contradictory sample sizes, contradictory results with identical sample sizes…" (63). Elsewhere in the stem cell arena, debate is in progress around similar analyses that raised important questions (64–67). These issues heighten our concerns about the adequacy and accuracy of some clinical trial design and reporting, concerns that are not limited to the stem cell field, but are noted in a diversity of clinical trials (68).

**Clinical stem cell studies: can we separate signals from noise?** On the basis of current knowledge and the uncertainties generated as studies are questioned or retracted, we might ask why clinical stem cell trials should be continued, and if so, how? An affirmative response to "why" would likely cite a number of reported successes, with the bar for success set rather low in many cases. Context can be found in Ioannidis' examination of 45 clinical research studies (59), albeit none of them used stem cells. Although all claimed efficacy, 32% were either contradicted or their reported magnitude of effect was unsubstantiated by later studies. Ioannidis highlighted the uncertain validity of small trials (59), a concern also applicable to stem cell studies.

One means for dealing with concerns regarding small trials is to perform a meta-analysis. However, it is critical to remember that meta-analyses are not intended to replace the determinism acquired from adequately powered, carefully designed prospective trials. Rather, their primary intent is to determine whether merging data from homogeneously designed studies with outcome signals too underpowered to yield definitive conclusions provides a more robust statistical outcome. Achieving such an outcome is considered justification for the design and execution of larger prospective trials. To maintain meta-analytic validity, the rules of meta-analysis include rigid comparability in design, execution, and analysis of the included studies. When multiple studies report

partly conflicting or weak signals while amplifying the outcome signal, a meta-analysis may oversimplify and lead to inappropriate conclusions. In addition, an evaluation of properly designed meta-analyses that led to performance of definitive trials demonstrated that the outcomes of these trials did not recapitulate the suggestions from the meta-analyses in 35% of the comparisons (69).

An example is provided by a meta-analysis of 2,625 patients in 50 cardiac stem cell studies, which include 2 study designs, 3 cell types, and a wide range of sample sizes, cell numbers, modes of administration, and follow-up periods (70). Subgroup analyses indicated that the cell therapies were associated with persistent improvements in LV function and remodeling in cardiomyopathy and AMI, and reduced mortality and recurrence of AMI and stent thrombosis, with no increase in adverse events (70). However, the positive signal sizes were modest (e.g., the increase in LVEF and decrease in infarct size averaged a physiologically marginal 4%). The authors concluded that their meta-analysis revealed signals warranting further long-term, large clinical trials. Because the effect is durable and prolonged, greater increments in outcome signals may be revealed after longer-term follow-up. That larger long-term trials are justified might be a fair conclusion for the larger studies dominating the statistics, but not necessarily for smaller studies included in the meta-analysis.

A different message came from a meta-analysis of 30 randomized controlled trials comprising 2,037 patients (71). BMMCs, MSCs, or other specialized cell types were delivered by intracoronary infusion after AMI. In the 22 BMMC trials included, there was no significant functional improvement, nor was there any difference between BMMCs and other cell types. This is consistent with a recent trial showing that intramyocardial stem cell administration has a better outcome than intracoronary (29), and may explain why the meta-analysis incorporating both administration routes met with a significant, but physiologically unimpressive, functional improvement (70).

## "PATIENTS ARE DYING AND ARE DESPERATE TO LIVE: IN THAT SETTING THEY SHOULD BE AVAILED OF EXPERIMENTAL STEM CELL THERAPIES…" (6).

**Balancing patients with patience.** That some dying persons are desperate to live is an eternal truism. It is equally obvious that people whose morbidities impair quality of life may desperately seek relief. Yet, the link between these challenges and access to conceptually new therapies (whether stem cell or any other experimental therapy for life-limiting disorders) is historically complex. There is an important distinction between data generated from compassionate use of a new therapy that is conceptually sound, but of unproven efficacy, and accumulation of efficacy data that goes beyond proof of concept and leads to scientifically-reliable therapeutic strategies. If desperate use in the guise of small observational studies far outpaces valid randomized clinical trials, the potential for medical/scientific harm emerges, with potential for either overstatement or understatement of efficacy, or delayed general acceptance of a rational therapy because of the nature of scientific support. An example is the 16-year hiatus between the first clinical implant of an ICD and publication of the first properly-controlled trial supporting its efficacy (72). Certainly, there is a point in the development of new therapies for extreme diseases where small initial observations are needed; the challenge is knowing when proof of concept should lead to prompt clinical trial designs. Part of the problem derives from taking comfort in our prior or current successes without fully appreciating remaining barriers, and part is impatience to move ahead aggressively on the basis of leads that science and technology dangle before us, before conclusive science emerges.

**Paramedical influences—innovation and impatience.** Although not alone, the medical segment of society feels a sense of urgency to advance innovation as quickly as possible. Diverse stakeholders contribute to this sense of urgency (8,51,73,74). At the center are patients, who are often led to expect effective therapy. They are surrounded by investigators seeking to remain competitive by translating hypothesis into proof; institutions focusing on recognition to support fundraising from industry, philanthropy, or grants; federal funding agencies seeking the best use of limited monies while answering to Congress (and Congress to its constituencies); and corporations and investors viewing the entire system as including a pathway to profit. All are reviewed by the media, which tell their stories with varying degrees of accuracy.

None of these paramedical influences is inherently bad. But if the goal is to move forward as quickly as possible, there should be systems in place to modulate the interaction between these stressors and the scientific community's responses. For the cardiac stem cell initiative, this goal is best addressed by focusing on which conclusions are valid on the basis of prior studies, and considering appropriate investigative and clinical application strategies going forward.

Undoubtedly, there are specific clinical circumstances in which stem cell therapy is justified; but in others, the sense of "now" should not precede the accumulation of reliable scientific data. The obvious distinction is between end-stage patients for whom no other reasonable option is available versus the use of stem cell therapy to prevent evolution of adverse remodeling. In the former, uncontrolled observational therapy may be acceptable; for the latter, at our current state of knowledge, uncontrolled studies are scientific transgressions. Although it might be argued that the myocardial substrate in end-stage and near-end-stage patients might offer an environment hostile to stem cell therapy, several trials ([20,29], and reviewed in Telukuntla et al. [8]) suggest that patients with low ejection fractions can and do respond well.

**"THE FIELD IS SUFFICIENTLY MATURE THAT WITHIN 3 TO 5 YEARS STEM CELLS WILL HAVE FAVORABLY ALTERED THE CLINICAL COURSE OF MAJOR CARDIOVASCULAR DISEASE" (6).** This prediction, made 10 years ago, did not come to pass. Nor are we particularly optimistic that it will happen in the next 3 to 5 years, although we acknowledge that it might. Medicine has seen sudden surges in progress where none might have been anticipated. But unless or until that surge happens, the landscape we face will remain challenging.

**FACING THE CHALLENGE: MODELS FOR TRANSLATING STEM CELL RESEARCH GOING FORWARD.** Although an overview of the potpourri of trial designs, cells, patient numbers, disease states, modes of cell administration, and follow-up gives conflicting signals, one inescapable message appears to be driving investigators and clinicians: namely, that there may be a needle worth pursuing within the haystack of stem cell strategies and related complexities. Yet, despite all we know about stem cells from pre-clinical studies, they still represent something of a black box in comparison with the levels of information we demand before testing chemically synthesized substances in patients. Given this situation, how might we go forward?

**Back to the starting line—approaching clinical trials "from scratch".** If we could backtrack to a time when no clinical stem cell trials had yet been done, we might commence with 2 broad strategies: 1) "rebuilding" hearts acutely depopulated of myocytes, which is happening currently in pre-clinical studies using cardiac fibrous skeletons seeded with cells to re-establish functionally contracting hearts (75,76); and 2) using implanted cells or cells mobilized from endogenous stores to repopulate myocytes in a damaged heart. This is the basis of most current effort.

A next step would be basic cellular and animal studies to identify whether specific cells and delivery methods are appropriate for specific diseases or whether a "one size fits all" concept is rational. The observation that human MSCs can be transplanted allogeneically into patients without eliciting an immune response (49,77,78) supports the latter approach. Whether using MSCs or other cells, it would be important to standardize cell identification, selection, preparation, and administration before clinical translation. Furthermore, if, as reported (65), a noncardiac source consistently gives rise to cardiopoietic cells, standardization of such a source would be warranted.

Subsequent clinical testing would first require standardization of trial design. Benefit would come from marrying a therapy for which one has significant understanding with a disease for which a positive response is likely. Initial studies could be performed in limited numbers of patients to acquire data that are hypothesis-generating and useful in preparing more rigorously designed, larger clinical trials for definitive hypothesis testing (79).

**Standardization: biological activity and efficacy.** Some questions raised in reviewing clinical trials derive from lack of rigorous standards *across* laboratories for obtaining, developing, maintaining, and assaying cell lines. Recognition of this issue prompted a National Institutes of Health panel to recommend establishing an MSC line or lines to serve as reference standards (52). Regrettably, this comes at a later than optimal time, because considerable effort and money have been and continue to be expended on a variety of cell lines of uncertain potential clinical impact. In addition, by restricting focus to MSCs, the opportunity to establish standards for other cell types remains wanting. Finally, there is not yet a "solid theoretical basis for using MSCs as broad therapeutics" (52), leading to concern that it may be premature to proceed with standardization (52). Nonetheless, as cell lines are reported from multiple sources, some basis for comparison with a standardized population would be useful, if not essential.

**Guidelines and regulation.** In the United States, the Food and Drug Administration regulates stem cell development as a therapy; counterpart regulations exist in the European Union. The International Society for Stem Cell Research has published detailed recommendations in the format of a guidelines document (80). The issue is not any lack of thoughtful recommendations; rather, it is how they are interpreted and applied and how loopholes are exploited

in the march to translation. While guidelines for phase 2 trials in various fields are being examined and approaches to trials updated (81) and enacted (82,83), egregious efforts at circumvention continue, potentially challenging adherence to existing standards for administering untested therapies (e.g., 84–86).

Concerns about oversight and regulation also apply to small clinical studies not subject to governmental agency scrutiny. The International Society for Stem Cell Research recommends: *"Clinician-scientists may provide unproven stem cell-based interventions to at most a very small number of patients outside the context of a formal clinical trial"* (80), with a peer-review process conducted by "appropriate experts" to approve plans for the procedure.

One could argue that pioneering bone marrow transplants (e.g., 87) and other medical milestones justify unfettered access to "small numbers of patients" for investigators who have an idea they want to translate rapidly. Two problems are evident:

1. We have accrued voluminous data showing positive and negative trends with regard to cell therapy. Although we still need to have the best ideas translated to the patient, any intent to administer an unproven therapy to patients should be held to the most rigorous standards of peer review by individuals who not only "have no vested interest in the proposed procedure" (80), but who also hold to the highest standards of patient advocacy within the context of an Institutional Review Board (IRB).
2. Given the altered realities of the research university (88–90) such that business considerations are now strongly entrenched, if the individual proposing a study is a leading light and/or the institution understands the potential for publicity and funding deriving from performance of the study, IRB members who review and rule on the request may experience unintended pressures. In addition, some IRB members, themselves, may have the same apparent conflicts of interest that they are empowered to address in others under certain limited institutional circumstances (91). Although, for most matters, this concern does not apply to conventional institution-based IRBs, completely independent external IRBs are a potential solution when broader institutional interests create apparent conflicts.

**Facing the future: 2 new clinical approaches.** Two recent efforts intended to move exploration of cell therapy forward are noteworthy:

1. CCTRN (Cardiovascular Cell Therapy Research Network) rethinks the design of phase 2 trials, with Bayesian analysis considered as a means of ongoing assessment of trial direction and outcome (81). The FOCUS trial (46), reported by CCTRN investigators, exemplifies the appropriately designed trial. Its physiological outcome was marginal, not the "big bang" the field might have hoped for, but an accurate accounting of outcome.
2. BAMI (Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells on All-Cause Mortality in AMI) is a Phase 3 safety/efficacy all-cause mortality trial enrolling 3,000 patients "to test if the product and delivery method…can lead to a 25% reduction in mortality" (92). BAMI relies on intracoronary infusion of autologous bone marrow-derived progenitors: the outcome depends on this being "the right cell" and approach to administration, as well as a logistically demanding design in every step from patient selection through cell preparation, administration, and follow-up.

**I-SPY2, a different model for going forward.** This direction derives from the premise that, at least at the outset, experimental cardiac therapy should target those cardiac patients whose prognosis is not far different from those with many types of cancer. A potential model is the multicenter I-SPY2 (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And moLecular Analysis 2) phase 2 trial, evaluating neoadjuvant therapy delivered prior to breast cancer surgery (82,83). A 120-patient control group receives state-of-the-art therapy, while 5 simultaneous experimental treatment arms (120 patients each) are selected from multiple proposed protocols. Those treatment regimens showing "high Bayesian predictive probability of being more effective than standard therapy" will move forward, whereas those showing a low probability of improving efficacy will be discontinued and replaced by new drugs to be tested (82,83).

Consider the possibility of adapting the I-SPY2 trial design strategy to the cardiovascular stem cell challenge by designating an appropriate high-risk population, using current knowledge to identify the most promising cardiac stem cells for this population, and agreeing on administration and follow-up procedures. There might be 5, 10, or more different stem cell populations suggested for inclusion. Multiple hospitals independent of the institutions at which the cells were identified and developed would carry out the trial; the Bayesian analytic approach of I-SPY2 would be used. This potentially offers a more consistent, accurate, and rapid path to definitive answers than has occurred to date, and (at least initially) would require fewer patients as experimental

subjects. Although issues of intellectual property and jockeying among various business interests would require resolution, I-SPY2 suggests that these can be resolved and that the overall strategy has merit.

In going forward, it should be noted that issues regarding cell fate await resolution (28-45,82,83). Hence, future trials of various designs might more consistently avail themselves of imaging techniques to assess cell survival (28-31). Approaches such as these may not only allow the correlation of cell survival with functional outcome, but may also enhance prospects for personalizing therapy (28).

**CONCLUSIONS.** Although basic research continues, data central to the myocardial repair/regeneration effort have been retracted (23), while concurrently, the clinical validation process in cardiac repair/regeneration appears to be in danger of stalling. With few exceptions, numerous variations on the same study design are repeated, yielding variations on the same outcomes but with continued expectation of a different outcome. This situation perilously approaches a clinical dead end. In the interest of avoiding intrusions that do not benefit patients, new approaches including more centralized oversight, external peer review, and collaboration among groups translating cell therapy are desirable. We trust that the positive examples of collaboration and advancement to which we have referred (28-31,46,81-83,92) are steps in this direction.

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## NOISE, OPTIMISM AND DENIAL—PERSPECTIVES FOR RELIABLE DISCOVERY FROM STEM CELL THERAPY, RENAL DENERVATION, AND CARDIAC RESYNCHRONIZATION THERAPY

*Darrel P. Francis, MA, Graham D. Cole, MA*

*"It is difficult to get a man*
*to understand something…"*
—Upton Sinclair (93)

Science is the systematic step-wise process of replacing untrue beliefs with less untrue ones. A clinician consulting with an individual patient has different priorities. By blending scientific knowledge with the human skill of expressing information encouragingly, we help each patient achieve the best possible outcome. Clinician-scientists, who straddle this divide, have made substantial contributions. However, this merging of roles also has less-recognized dangers.

Experienced clinicians integrate disparate information to provide the best experience for patients. We learn that some variables (such as blood pressure and EF) vary randomly and largely meaninglessly between visits. We may handle this milieu of uncertainty by using clinical acumen to select those values most appropriate to the overall picture: the consequences for science are not a priority at the bedside.

In the previous section, Drs. Rosen and Myerburg have provided a thought-provoking and insightful account of the current situation and future challenges for cell therapy. A notable challenge is the contrast between reported efficacy in numerous unblinded or uncontrolled studies and high-profile neutrality in randomized, controlled, blinded conditions. In the present section, we discuss 3 common themes and suggest how readers can do better than passively riding the rollercoaster of excitement and disappointment.

**NOISE.** Although some biological variables do not change (e.g., date of birth) and others change only slowly and predictably (e.g., age), most change unpredictably between 1 measurement and the next. Cardiology is particularly vulnerable in this regard, because heartbeats are numerous and variable in intensity, responding to numerous internal fluctuations. For example, individual blood pressure or heart rate values may vary widely over seconds or minutes. On top of this are the challenges of summarizing a large mass of data from a patient as a single number (94,95). Different observers may do this differently, which we may falsely attribute to lack of skill on the part of the junior observer. In reality, even experienced observers may not realize they are doing it differently when secretly given identical data twice (96).

Unlike drugs, which inevitably target multiple organs in the body, cell therapy hinges on improving cardiac function; thus, assessing cardiac function is important. With relatively low event rates in patients entering clinical trials, the number of patients required to observe a morbidity-mortality benefit may be challengingly large for nascent therapies, and so phase II trials with imaging endpoints are a logical method of screening and refining cell therapy technologies. Sadly, relatively little attention is placed on ensuring that this cardiac function evaluation minimizes noise and its deadly counterpart element, namely, the bias of optimism.

**OPTIMISM.** Optimism drives us forward in clinical research, but may also, paradoxically, be silently

holding us back. Our statistical methods rely on noise to be in random directions. Clinical trials enroll multiple patients to make the random variations cancel each other out. More patients provide more certainty that pure random to-and-fro variation will average to approximately 0.

The left column of **Figure 2** illustrates this in 6 imaginary patients who have received an ineffective therapy. Their individual random increases and decreases tend to average to approximately 0. When individual patient noise is larger (second column in **Figure 2**), there is still no reason for the average result to be tilted 1 way rather than the other. However, introducing optimism, for example, by choosing the more favorable of 2 acquired values for each patient (third column in **Figure 2**), gives the average a directional tendency. With optimism, greater noise produces a greater false-positive effect (fourth column in **Figure 2**). Statistical significance testing of pre- versus post-values will be falsely exciting because noise-with-optimism is a real statistically significant increase. Unfortunately, it is not a real benefit.

Neither noise nor optimism alone can cause this problem: it is the combination that is deadly (97,98). Yet, they could not mislead us, even together, if we recognized the need for a randomized controlled trial with concealment of the allocation arm. This makes the bias equal in both arms and therefore neutralizable by calculating the net benefit (99) of therapy as the difference between the arms. The real threat is noise and optimism combined with a third element, denial.

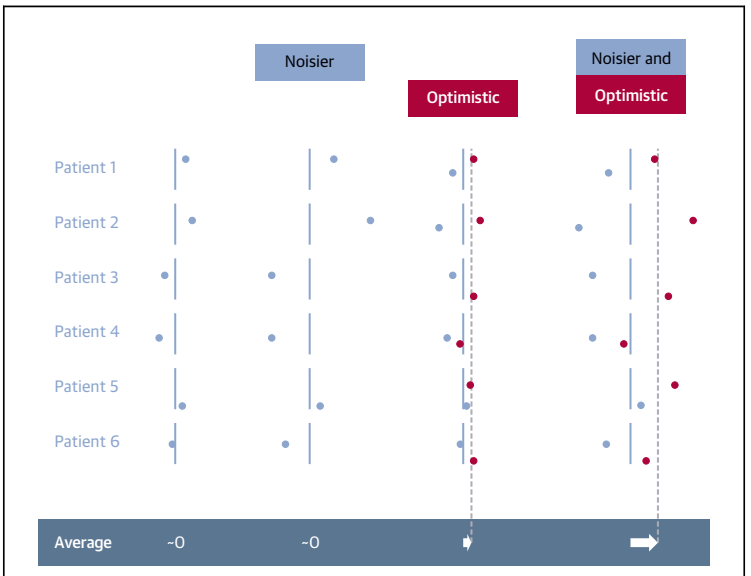


**FIGURE 2 How the Size of Random Noise and the Presence of Bias Toward Optimism Interact to Generate Statistically Significant, But False-Positive, Results**

Each **data point** is the measured improvement in a single patient of a clinical variable after a therapy (which happens to be ineffective). Across all patients, the average change is 0, but only if the measurements are acquired dispassionately. If, for example, 2 measurements are made and the "best" is chosen **(red data points)**, this optimism contributes a positive bias **(arrow)** that may be (correctly) detected as statistically significant even though it is illusory. Noisier measurements are more vulnerable. Large study size paradoxically makes the problem worse (97,98).

**DENIAL.** As clinicians, we tend to accept the existence of noise and optimism in general, yet deny its importance in our own individual research fields or clinical practices. Almost all of thousands of congress attendees (100) in several countries told us that if blood pressure seemed not to have fallen after initiating 1 ordinary antihypertensive tablet, they would remeasure it, hoping for a lower value. For a therapy widely publicized to have a very large effect, such as 30 mm Hg, the powerful expectation might limit acceptance to only the lowest values.

When automated measurements showed a much smaller effect, our community seemed determined to deny that they might be more reliable. One explanation offered was that drug trials had always shown office pressures to drop more than ambulatory pressures (101). However, this is only true for unblinded trials, that is, with office pressures measured by staff knowing which trial arm the patient is in. When staff members are blinded, office and ambulatory measurements show identical effect sizes (101). Thus, the rarely discussed insight from drug trials is that, unless protected by blinding, we cannot help overstating office blood pressure reductions in the active arm, because we are only human. When the large *blinded* randomized controlled trial of renal denervation found a far smaller blood pressure effect than previous *unblinded* studies, the most likely explanation was that blinding had prevented inadvertent overstatement (98). Yet, expert analysis in our community professed confusion (102) "at the higher level" and proposed one-half dozen explanations that ignored the bias-resisting benefits of *blinding*. This could be a sophisticated, articulate, and expert example of denial.

**WHY IS GETTING A WRONG ANSWER HARMFUL?** First, scientists or investors relying on published science may unknowingly embark on a futile path. Drs. Rosen and Myerburg boldly highlight that "the clinical validation process… appears to be in danger of stalling."

Second, frequent, but superficial, public discussion of positive results progressively entraps all

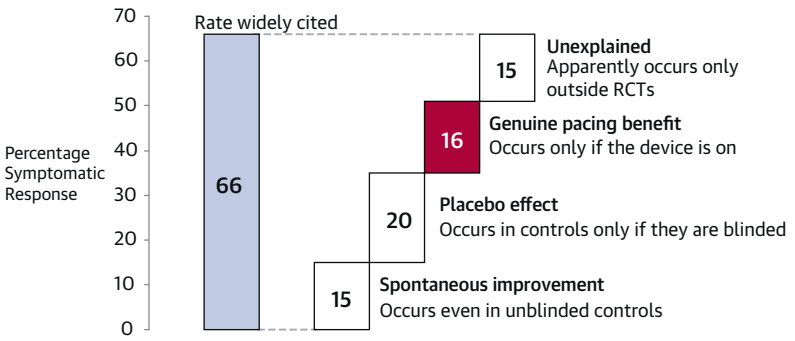


**FIGURE 3 Contributors to the 66% Symptomatic Response Widely Described for Cardiac Resynchronization Therapy**

Within randomized controlled trials (RCTs), the response rate in the active arm averages 51%. Placebo control arms (which receive a device but not cardiac resynchronization therapy pacing) show a response rate averaging 35%, indicating the incremental effect of pacing to be 16 percentage points. The control subjects in blinded trials report a better response than those in unblinded trials: we can use this to estimate the size of the placebo effect of device implantation. The response in the unblinded controls is not due to pacing or implantation placebo, and might be described as spontaneous improvement. Figure prepared based on data from Sohaib et al. (104).

participants in cognitive dissonance (103), that is, increasing difficulty countenancing the possibility that the effect is illusory.

Third, when our entire community tacitly accepts optimistic estimates as a convention, real scientific progress can come to a halt.

The serious impediment to progress comes from the differential ease of expanding the component rectangles in **Figure 3** (104). Suppose an exciting report arises of an unblinded cohort experiencing a high response rate (e.g., 80%). This may represent a Nobel-prize-deserving near-doubling of the genuine benefit (red component in **Figure 3**) from 16% to 30%, or a slight enlargement of the other components from 50% to 64%. Which will occur more commonly? What innovations will thereby accumulate into the "state of the art?" Is it, therefore, wise for our field to define progress by expansion of total response rate in unblinded, uncontrolled cohorts? The parallel in cell therapy, elegantly highlighted by Drs. Rosen and Myerburg, is that despite years of effort, we still do not know which cell type to use.

The challenges are not insoluble. For example, individual patient response quantification methods can minimize noise (105), and automation can reduce the bias of optimism (106). However, overcoming the third element, denial, requires clearly contradicting an apparent expert consensus. This can be an uphill struggle (107), and unfortunately, cannot be automated.

**A WAY FORWARD.** There are many excellent scientists working in these fields. Drs. Rosen and Myerburg present a thoughtful, expert survey of potential improvements in trial design. At a more general level, we should move forward from denial that randomization and blinding are important. We should also be supportive of colleagues who wish to change their public positions; otherwise we, too, are contributing to research error.

A curious feature of cell therapy trials is that reports with higher objective rates of arithmetically or logically impossible features show more positive efficacy (22). Although none of us can eradicate errors from our work, we should prevent errors in effect size measurement, especially the predictable bias toward false appearance of benefit.

As Drs. Rosen and Myerburg stated, to dilute the effect of being a personal stakeholder in the intellectual or academic property of 1 therapy, an efficient solution is to test several therapies. The I-SPY2 protocol is an excellent example. This design has not proven popular with corporate cell therapy funders who wish to have total control (for whatever reason), but it may be the best way for patient volunteers to be sure they are contributing to improvements in treatment.

Our final proposal resolves a dilemma. Researchers will always want to spin data favorably to obtain employment advancement (or even merely continuation), secure funding (academic or industry), or progress on the medicopolitical society ladder. The challenge is to allow this, but insulate ordinary scientific readers seeking reliable information who may stumble across the paper. Perhaps a code word could be inserted for readers to recognize a paper as not intentionally misleading but merely optimistic marketing deserving poetic license? We suggest 3

terms already beginning to be used in this way: "emerging," "nascent," and "exciting."

## CELL THERAPY FOR HEART DISEASE: A GLASS HALF FULL

*Eduardo Marbán, MD, PhD*

In their review of stem cell research as applied to heart disease, Drs. Rosen and Myerburg emphasize the dashed expectations of the last decade: the retractions, the exaggerations, and the fits and starts. My own view of the status of the field is more positive. The path has not been linear, nor should the oft-shameful history of cardiac cell therapy be taken as a roadmap for scholarly translation. Nevertheless, remarkable progress has been made. Indeed, in reflecting upon the field, I have identified 6 major emergent insights that have the potential to shape future progress (108). By way of a counterpoint to the previous section, I will consider each of these emergent insights as tangible examples of forward movement.

**1. ESTABLISHMENT OF SAFETY WITH INTRACORONARY DELIVERY.** In 2001, an AMI patient was treated by injection of autologous BMMCs down the infarct-related artery (109). Although the scientific basis of this human experiment was (and remains) shaky (110,111), the paradigm has often been repeated and collectively forms the basis for the largest clinical experience to date with cell therapy for heart disease. Although notable for extraordinary safety, the experience has resulted in little by way of changes in surrogate endpoints such as EF, scar size, or myocardial perfusion (108). Importantly, manufacturing details can influence the potency of BMMCs. This may explain why, although their safety record has proven superior, intracoronary BMMC trial results have been so variable (112,113). The lack of excess arrhythmias in BMMC-treated patients (unlike earlier experience with skeletal myoblasts) is particularly notable (114). Although BMMCs are the only cell type for which large numbers of patients are available, thus far, the general pattern of safety with intracoronary delivery has also held up with other cells (19,54,56).

**2. DEMONSTRATION OF THERAPEUTIC REGENERATION.** Regeneration, defined as "regrowth of lost or destroyed parts or organs" (115), is often misused to describe functional improvement or loss of scar tissue. Human BMMC studies that reported reductions in scar size (116) show only small scar mass reductions with no reciprocal increases in living heart muscle. Such changes may reflect a salutary decrease in the extent of injury, but not regrowth of destroyed parts. However, recent results in humans with cardiosphere-derived cells (CDCs) do give reason to believe in the possibility of therapeutic regeneration. CDCs are stem cells in that they exhibit multilineage potential and clonogenicity (117,118), but they work through indirect mechanisms (119). The CADUCEUS trial (19,54) tested the safety and efficacy of intracoronary autologous CDCs in 17 patients with LV dysfunction and a recent myocardial infarction (MI) (1.5 to 3 months prior), compared with 8 routine-care control subjects. The subjects who received CDCs (but not the control subjects) experienced sizable increases in the amount of viable myocardium over 12 months of follow-up. CADUCEUS was the first controlled clinical trial to demonstrate an increase in viable tissue as a result of cell therapy (19,54). On the basis of the interpretation of gadolinium-enhanced cardiac magnetic resonance scans, it was concluded that cardiac regeneration had occurred; we went on to validate this interpretation in pigs treated with intracoronary CDCs by directly comparing cardiac magnetic resonance imaging with tissue histology (120). The regrowth of lost heart muscle in response to treatment provides proof of the concept of therapeutic regeneration (121), even in the setting of an "irreversible" myocardial scar.

**3. THE RISE OF ALLOGENEIC CELL THERAPY.** The prevalent autologous paradigm has the advantage of avoiding immunologic rejection, but because of patient-specific tissue harvesting, cell processing, and quality control, it imposes significant risk, expense, and inflexibility. In addition, cell efficacy may vary with donor age and comorbidities. The use of allogeneic cells, if safe and effective, would bypass such limitations, enabling the generation of "off the shelf" cell products. However, whether or not it poses safety hazards, the risk of immune rejection may limit effectiveness unless rejection occurs after the cells have exerted their beneficial paracrine effects (119,122,123). Allogeneic MSCs or their precursors have been used in various early-phase human trials of MI and heart failure, with no safety concerns reported to date (124). On the basis of findings that allogeneic CDC transplantation without immunosuppression is safe, promotes cardiac regeneration, and improves heart function in rats (123) and pigs (120) with MI, the ALLSTAR (Allogeneic Heart Stem Cells to Achieve Myocardial Regeneration) trial of allogeneic CDCs post-MI is currently in progress (55). The increasing recognition that allogeneic therapy may be safe and effective reflects an important turning point for the field.

**4. INCREASING MECHANISTIC INSIGHTS.** The canonical mechanism of stem cell therapeutics posits

that injected cells will engraft, proliferate, and differentiate, thereby repopulating the injured heart (125). However, despite poor retention and minimal long-term survival of transplanted cells, cell transplantation often produces beneficial effects (126). How can cells that disappear produce lasting benefits? Multiple lines of evidence now indicate that the beneficial effects of transplanted CDCs are mostly indirect (119); in the extreme, allogeneic CDCs are cleared completely within several weeks, but their functional and structural benefits persist for at least 6 months (123). Thus, long-term transplanted cell survival is not required for sustained benefit. This appears to be true for many other nonpluripotent cells (108,122). Much attention is being (correctly) devoted to identifying the key factors responsible for indirect benefits; exosomes are among the contenders (127). Whatever the mediators turn out to be, there has been a major conceptual shift from canonical stem cell-based mechanisms to the notion that most clinically-applied cells work indirectly (128), opening new prospects for next-generation cell-free products and rationalizing the use of allogeneic cells.

**5. GLIMMERS OF CLINICAL EFFICACY.** The BMMC experience has yielded little evidence of benefit in surrogate endpoints such as EF and scar size (129). Nevertheless, it is intriguing that significant improvements in clinical endpoints have been reported. The REPAIR-AMI (Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction) study demonstrated favorable clinical outcomes associated with BMMC therapy, sustained at 5 years of follow-up (130), at which time the composite endpoint of death, MI, or revascularization exhibited an odds ratio of 0.62 in favor of the BMMC-treated group relative to placebo ($p = 0.03$). Clinical outcome trends in favor of BMMNC therapy have also emerged from meta-analyses (131,132). Interestingly, the greatest benefits of cell therapy occur in patients with the most extensive MI-induced damage. For example, in the Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) (133), Finnish Stem Cell Study (FINCELL) (134), and REGENT (Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction) (135) studies, the major determinant of functional recovery after BMMC therapy was low baseline EF. This finding suggests that cell therapy trials might benefit by targeting a sicker patient population (129). The increasing recognition that BMMCs may have clinical benefits, despite little signal in terms of surrogate endpoints, gives reason to hope that emerging cell types, with greater effects on scar size or EF, will have even more notable clinical benefits.

**6. PROGRESSION TO PHASE 2 AND 3 STUDIES.** In cell therapy (as in many other fields), larger studies often fail to confirm promising early-phase trial results (136). Well-powered, rigorously-designed clinical trials, focusing on hard clinical endpoints, are needed to determine whether changes in surrogate endpoints (e.g., scar size, ventricular volumes, and EF) translate into increased survival and reduced morbidity (129). Fortunately, several such trials are in progress (114), including the phase 3 BAMI trial of BMMCs (92). The progression from small observational studies to larger studies focusing on clinical endpoints reflects gradually increasing interest in specific therapeutic candidates by commercial entities. The review by Rosen and Myerburg castigates "paramedical influences," but without commercial development, the potential of the field will never fully be clarified, nor will the wide dissemination of reliable products be possible.

**CONCLUSIONS.** Based on the previously mentioned considerations, over the last several years, it is evident that we have developed a solid basis for moving forward. Blessed to date by prevalent safety, we (fortuitously) managed to avoid the sort of debacle that derailed gene therapy for more than a decade (137). The demonstration that therapeutic regeneration can happen, in a setting where conventional wisdom teaches that the loss of living tissue is irreversible, catapults the field onto a new plane yet to be reached by any other treatment approach. Mounting evidence that allogeneic cells can be safe and effective is consistent with mainstream product development paradigms. Increasing insights into the mechanism of action of cell therapy provide waypoints to help us set priorities for future work on the basis of what is and is not rational. Intriguing glimmers of clinical efficacy in trials to date, coupled with the increasing number of advanced-phase clinical studies currently in progress, give further reasons for cautious positivity.

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